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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,664	02/18/2004	Felix A. Montero-Julian	BECK1130-2(2052-183)	5199

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/782,664	MONTERO-JULIAN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 8/23/04,3/27/07,11/13/06,7/29/04.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-78 is/are pending in the application.

4a) Of the above claim(s) 7,8,15,16,23,24,32,33,40,41,48,49, 51-72 and 78 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6,9-14,17-22,25-31,34-39,42-47,50 and 73-77 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 18 February 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 8/23/04 and Applicant's responses filed 3/27/07, 11/13/06 and 7/29/04 are acknowledged and have been entered.

2. Applicant's election of Group I (claims 1-50 and 73-78), and species of HLA-A2/β2m/MART-1 as the MHC/template peptide complex in Applicant's responses filed 3/27/07 and 11/13/06 is acknowledged. In addition, Applicant's election of the species 100X molar excess of competitor peptide, incubating the sample for about 2-20 hours at about 21 degrees C, HBc 18-27 tagged with FITC as the tracer peptide, only one competitor peptide is used and soluble HLA molecule in Applicant's response filed 3/27/07 is acknowledged.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 1-6, 9-14, 17-22, 25-31, 34-39, 42-47, 50 and 73-77 read on the elected species.

Accordingly, claims 7, 8, 16, 15, 23, 24, 32-33, 40, 41, 48, 49, 78 (non-elected species of Group I) and claims 51-72 (non-elected Group II) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-6, 9-14, 17-22, 25-31, 34-39, 42-47, 50 and 73-77 are currently being examined.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6, 9-14, 17-22, 25-31, 34-39, 42-47, 50 and 73-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V.

Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method for identifying an MHC binding peptide for a *modified* MHC monomer, said method comprising the method steps recited in the instant claims.

The instant claims are drawn to a method for identifying an MHC binding peptide for a modified MHC monomer, wherein the modified monomer has a template MHC binding peptide bound thereto, and a system comprising said modified MHC monomer. As such, the claims are drawn to an MHC monomer of partially disclosed structure.

The instant specification discloses at [0044] that "As used herein, the terms "modified MHC monomer" and "modified HLA monomer" refer to class I monomers as described above, but which have been engineered to introduce modifications as described below. These terms also encompass functional fragments of the MHC monomer that maintain the ability to assemble into a ternary complex with an appropriate MHC-binding or HLA-binding peptide and beta-2 microglobulin under renaturing conditions and to dissociate under denaturing conditions. For example, a functional fragment can comprise only the alpha 1, alpha 2, alpha 3, domains, or only alpha 1, alpha 2 domains, of the class I heavy chain, i.e., the cell surface domains, that participate in formation of the ternary complex. In another embodiment, modified MHC monomers can be class I heavy chain molecules, or functional fragments thereof, contained in a fusion protein or "single chain" molecule and may further include an amino acid sequence functioning as a linker between cell surface domains of the monomer, a detectable marker or as a ligand to attach the molecule to a solid support that is coated with a second ligand with which the ligand in the fusion protein reacts. Moreover the terms "modified MHC monomer" and "modified HLA monomer" are intended to encompass chimera containing domains of class I heavy chain molecules from more than one species or from more than one class I subclass. For example, a chimera can be prepared by substitution of a mouse beta-2m for human beta-2m in a human HLA-A2 monomer."

The instant specification further discloses at [0051] that "This invention provides amino acid sequence modification of MHC monomers prepared with various objectives in mind, including increasing the affinity of the subunit for antigenic peptides and/or T cell receptors, facilitating the stability, purification and preparation of the subunits. The monomers may also be modified to modify plasma half-life, improve therapeutic efficacy, or to lessen the severity or occurrence of side effects during therapeutic use of complexes of the present invention. The amino acid sequence modifications of the subunits are usually predetermined variants not found in nature or naturally occurring alleles. The variants typically exhibit the same biological activity (for example, MHC-peptide binding) as the naturally occurring analogue. "

Thus, the specification discloses that many different modification objectives are envisioned in producing a modified MHC monomer. The instant claims recite that the modified MHC monomer has bound thereto a template MHC binding peptide, but do not

recite functional properties of the binding, nor which biological activity/ies of the non-modified MHC molecule(s) is/are retained by the modified monomer, nor which functional property/ies of the modified monomer are desired.

One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-6, 9-14, 17-22, 25-31, 34-39, 42-47, 50 and 73-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 73 is indefinite because it is not clear what is meant, *i.e.,* it appears to be missing a portion of the claim and is missing a period at the end.

b. Claims 1, 26 and 73 are indefinite in the recitation of "modified MHC monomer" because it is not clear what is meant, *i.e.,* what the metes and bounds of the said claims are.

c. Claims 73-77 are indefinite in the recitation of "system" because it is not clear what is meant.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2, 4, 5, 10-12, 18-22, 25-27, 29, 30, 35-37, 43-47 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Celis *et al* (PNAS USA 1994, 91: 2105-2109) as evidenced by Henderson *et al* (PNAS USA 1993, 90:10275-10279) and Springfrog (2007).

Celis *et al* teach an MHC peptide binding assay for determining relative affinity using purified HLA-A1 MHC class I molecules incubated with a labeled standard peptide of 9 amino acid residues in length and a competitor test peptide (in about the 10 uM to 1 nM range, and of 9 to 10 amino acid residues in length), for 2 days at room temperature in the presence of exogenous β2m, and determining a difference in signal produced by the detectable label as compared with the signal produced by the monomer after the incubation, *i.e.,* determining the percent MHC-bound radioactivity, and wherein at least a portion of the competitor peptide exchanges with the endogenous peptide present in

the HLA-A1 monomer, and wherein the competitor peptide is tested for MHC specificity (see entire article, especially Materials and Methods section and Results section).

Evidentiary reference Henderson *et al* teach that a specific cell surface MHC allele-type molecule can bind up to 2,000 different endogenous peptides (especially Introduction section).

Evidentiary reference Springfrog teaches that normal room temperature is about 22 degrees C.

Although the art reference does not explicitly teach "at least one MHC monomer...having bound thereto a template MHC-binding peptide," the art reference teaches that the MHC class I molecules are isolated from an HLA-A1 positive homozygous lines, and said line processes and expresses an endogenous peptide in the peptide binding groove of MHC molecules, *i.e.,* each has a "template" peptide bound thereto. Therefore, the MHC monomer recited in the claimed method appears to be the same as the MHC monomer of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the method of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Although the art reference does not explicitly teach "wherein the template peptide has lower or intermediate affinity as compared with the tracer peptide for the monomer," the art reference teaches there is peptide exchange and measurement of radioactively labeled tracer peptide. Therefore, the claimed method appears to be the same as the method of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the method of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).
The instant claims are included in this rejection because the art reference teaches that peptide exchange does occur and the assay is conducted in the presence of exogenous β2m which will facilitate peptide exchange; thus the art reference meets the limitation recited in instant claims 1 and 26 "wherein the template peptide has lower or intermediate affinity as compared with the tracer peptide for the monomer" and also meets the limitation recited in instant claim 26 "wherein at least a portion of the first competitor peptide exchanges with the template peptide."

With regard to the limitation recited in instant claims 4 and 29 "wherein suitable liquid phase conditions include incubating the sample for about 2 to 20 hours," the art reference teaches incubating 2 days or 48 hours, and so meets the claim limitation.

With regard to the limitation recited in instant claims 5 and 30, "wherein the suitable liquid phase conditions further include incubating the sample at about 21 degrees C," the art reference teaches incubating at room temperature or at about 22 degrees C, and so meets the claim limitation.

Although the art reference does not implicitly teach that the excess of the first competitor peptide is about 100-fold molar excess, the art reference teaches a competitor test peptide in about the 10 uM to 1 nM range, and the evidentiary reference teaches that a specific cell surface MHC allele-type molecule can bind up to 2,000 different endogenous peptides. Therefore the method step of "wherein the excess of the first competitor peptide is about 100-fold molar excess" recited in the method of instant claims 2 and 17 appears to be the same as that in the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on applicant to show a distinction between the method of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim 25 is included in this rejection because the art reference teaches determining the MHC specificity of the competitor peptide.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 6, 9, 26, 31, 34, 73, 74 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Celis *et al* (PNAS USA 1994, 91: 2105-2109) in view of U.S. Patent No. 5,734,023 and Gerristsma *et al* (Blood, 2001, 98(11) Part 1, pp 404a-405a, abstract).

Celis *et al* teach an MHC peptide binding assay for determining relative affinity using purified HLA-A1 MHC class I molecules incubated with a labeled standard peptide and a competitor test peptide (in about the 10 uM to 1 nM range, and of 9 to 10 amino acid residues in length), for 2 days at room temperature in the presence of exogenous β2m, and determining a difference in signal produced by the detectable label as compared with the signal produced by the monomer after the incubation, *i.e.,* determining the percent MHC-bound radioactivity, and wherein at least a portion of the competitor peptide exchanges with the endogenous peptide present in the HLA-A1 monomer, and wherein the competitor peptide is tested for MHC specificity (see entire article, especially Materials and Methods section and Results section).

Celis *et al* do not teach wherein the tracer peptide has a detectable label that is a fluorophore (claims 6 and 31) such as fluorescein (FITC) (claims 9 and 34), nor a system for identifying an MHC-binding peptide such as that recited in instant claims 73, 74 and 77.

U.S. Patent No. 5,734,023 discloses adding an effector component to an MHC/peptide molecule, such a component being a labeling moiety such as fluorescein (especially column 15 at lines 27-30. U.S. Patent No. 5,734,023 further discloses formulating MHC molecules in kits, including for therapeutic or diagnostic uses, and discloses that any other reagents, such as detection reagents, be placed in a separate vial (especially paragraph spanning columns 28-29).

Gerristsma *et al* teach using a FITC-labeled HLA-A1 binding peptide and its use in a competition binding assay.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted a FITC-labeled tracer peptide such as taught by Gerristsma *et al* for the radioactively-labeled tracer peptide taught by Celis *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to make the assay safer and more convenient by replacing a radioactive label with a fluorescent label.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the MHC molecule taught by Celis *et al* along with the tracer peptide tagged with a detectable label, including one with a FITC label instead of the radioactive label taught by Celis *et al* in a kit as disclosed by U.S. Patent No. 5,734,023 for their MHC/peptide molecule and detection agent.
One of ordinary skill in the art at the time the invention was made would have been motivated to do this for ease of convenience in placing the components in a kit, and to make the assay safer and more convenient by replacing a radioactive label with a fluorescent label.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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